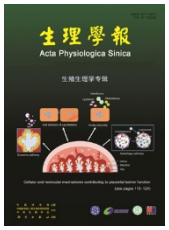

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综述

非侵入性电刺激神经调控技术：镇痛效果与镇痛机制

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摘 要：非侵入性神经调控技术是一种潜力巨大的非药物镇痛手段，具有经济、易操作、安全性高等优点，已被应用于各类临床疼痛的治疗。然而，目前仍缺乏对不同神经调控技术镇痛特性的深入理解。因此，本文从镇痛效果和镇痛机制两个方面入手，评述非侵入性外周神经电刺激(经皮神经电刺激、经皮迷走神经电刺激)和中枢神经电刺激(经颅直流电刺激、经颅交流电刺激)在镇痛方面的研究结果，总结各技术对急性疼痛和慢性疼痛的常用刺激参数和镇痛效果，探讨可能的镇痛机制。最后，本文对比和总结各技术的镇痛特点，讨论了现有研究的若干局限和未来的研究方向。克服这些局限将促进相关技术的临床应用，最终达到帮助患者缓解疼痛的目的，减轻疼痛对患者、其家庭和整个社会带来的健康和经济负担。

关键词：神经调控；镇痛；经皮神经电刺激；经皮迷走神经电刺激；经颅直流电刺激；经颅交流电刺激

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Non-invasive electrical neuromodulation techniques: analgesic effects and neural mechanisms

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Abstract: As non-pharmaceutical interventions, non-invasive neuromodulation techniques are promising in pain management. With many advantages, such as low costs, high usability, and non-invasiveness, they have been exploited to treat multiple clinical pain. Proper use of these techniques requires a comprehensive understanding of how they work. In this article, we reviewed recent studies concerning non-invasive electrical peripheral nerve stimulation (transcutaneous electrical nerve stimulation and transcutaneous vagus/vagal nerve stimulation) as well as electrical central nerve stimulation (transcranial direct current stimulation and transcranial alternating current stimulation). Specifically, we discussed the oft-used stimulation parameters, the analgesic effects on acute and chronic pain, and the neural mechanisms underlying the analgesic effect of each technique. We then contrasted the four kinds of nerve stimulation techniques, pointing out limitations of existing studies and proposing directions for future research. With more extensive and in-depth research to overcome these limitations, we shall witness more clinical applications of non-invasive electrical nerve stimulations to alleviate patients' pain and ease the crippling medical and economic burden imposed on patients, their families, and the entire society.

Key words: neuromodulation; analgesia; transcutaneous electrical nerve stimulation; transcutaneous vagus/vagal nerve stimulation; transcranial direct current stimulation; transcranial alternating current stimulation.

疼痛是现今社会一个重大公共卫生难题。据估计，慢性疼痛患病率高达20%~50% [1–5]，每年给我国造成的经济损失超过数千亿人民币[6, 7]。目前，药物是治疗慢性疼痛的主要手段之一。然而，阿片等镇痛药物存在潜在的风险，如近年来北美地区爆发的阿片危机，每一天都夺取上百人的宝贵生命(https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis)。在此时代背景下，寻找有效的非药物镇痛方法刻不容缓。

神经调控技术是一种潜力巨大的非药物疼痛治疗方法。该方法已被应用于临床疼痛的治疗。根据刺激电极放置过程是否有创，电刺激神经调控技术可分为侵入性电刺激(invasive electrical stimulation, iES)和非侵入性的经皮/经颅电刺激(transcutaneous/transcranial electrical stimulation, tES)两大类。前者包括深部脑刺激(deep brain stimulation, DBS) [8, 9]、侵入性迷走神经电刺激(invasive vagus/vagal nerve stimulation, iVNS) [10, 11]、脊髓电刺激(spinal cord stimulation, SCS) [12, 13]等；后者包括经皮神经电刺激(transcutaneous electrical nerve stimulation, TENS)[14, 15]、经皮/非侵入性迷走神经电刺激(transcutaneous/non-invasive vagus/vagal nerve stimulation, tVNS/nVNS)[10, 16]、经颅直流电刺激(transcranial direct current stimulation, tDCS)[17, 18]和经颅交流电刺激(transcranial alternating current stimulation, tACS)[19, 20]等。这两类神经调控技术都被证明有明显的镇痛作用。然而，iES 技术存在一些明显缺陷，如电极放置位置的组织容易感染，可能发生电极故障，维修和替换成本高等[21]，导致难以大范围推广应用。相比之下，非侵入性神经调控电刺激因其无创、安全性高、易操作且更经济的特点，得到了越来越多的关注。

本文将从镇痛效果和镇痛机制两个方面入手，评述非侵入性外周神经电刺激(TENS、tVNS)和中枢神经电刺激(tDCS、tACS)在镇痛方面的研究成果。本文将评估这四类技术对急性疼痛和慢性疼痛的镇痛效果以及不同刺激参数对镇痛效果的影响，并探讨其可能涉及的神经机制。在此基础上，本文对比和总结了各技术的镇痛特点，讨论了现有研究的若干局限和未来的研究方向。

1 非侵入性外周神经电刺激镇痛

1.1 TENS

TENS 通过置于皮肤表面的电极给个体施加电刺激，进而产生镇痛作用。根据刺激参数的不同，TENS 一般可分为高频低强度的常规 TENS (conventional transcutaneous electrical nerve stimulation, conventional TENS)和低频高强度的针刺样 TENS (acupuncture-like transcutaneous electrical nerve stimulation, AL-TENS) [22]。常规 TENS 的电极通常置于疼痛部位的同一皮节，刺激频率通常为 50~100 Hz，所施加的电流强度不会引起疼痛，因而引起的不适感较低；而 AL-TENS 对施加部位没有明显的限制，刺激频率通常为 1~4 Hz，所施加的电流强度常常在痛阈之上甚至达到疼痛耐受，因而较易引起不适感和不愉悦情绪[23, 24]。两者刺激参数的不同导致它们在镇痛效果、临床应用和镇痛机制上存在一定差异(表 1)。

1.1.1 镇痛效果

常规 TENS 对实验室诱发痛和部分临床慢性痛都有较好的缓解作用。Claydon 等人通过对 29 个实验研究进行 Meta 分析发现，超过半数的研究(55%)显示常规 TENS 可缓解机械和热刺激产生的诱发痛，且效应量为中等(0.5~0.79)到大(0.8 以上)[25]。临床研究显示，常规 TENS 不仅能有效缓解慢性疼痛(如癌痛[26]、慢性腰背痛[27]和原发性痛经[28])、分娩痛[29, 30]以及术后痛[31]等临床疼痛，还有助于恢复身体机能。一般来说，常规 TENS 只有局部或节段镇痛作用，因此电极片需要贴在患者疼痛部位附近[32]或同一皮节内[24]才有效。

相比之下，AL-TENS 具有更强的镇痛效果以及更广的镇痛范围[24]。AL-TENS 同样对实验室诱发疼痛(如热痛[33]、压痛[34]和激光诱发痛[35])以及慢性疼痛(如慢性腰背痛[36]、纤维肌痛[37])和术后痛[31]等临床疼痛有缓解作用。不仅如此，AL-TENS 的镇痛效果具有时间上的持续性[38]和空间上的全局性[35]。值得一提的是，当患者对常规 TENS 产生耐受时，AL-TENS 依然可以起到镇痛作用[38]。然而，AL-TENS 的镇痛效果似乎受到患者自身情况的影响。临床研究显示，AL-TENS 对于长期服用阿片类药物的患者没有显著的治疗效果，而只对非长期服用阿片类药物的患者有镇痛作用，但常规 TENS 的镇痛效果不受患者是否使用阿片类药物的影响[39]。

除了单独施加某类 TENS 外，也有研究考察了不同部位同时施加不同类型 TENS 即双位点刺激的镇痛效果[40]。Fujii-Abe 等研究显示，相比单纯的高强度电刺激[(31.3 ± 5.76) V]或低强度电刺激[(22.0 ± 7.49) V)，高-低强度组合刺激下体感诱发电位(somatosensory evoked potentials, SEPs)响应更小，且被试的疼痛强度评分更低[41]。Claydon 等人探究了刺激频率（高/低）、刺激强度（高/低）、刺激部位（同皮节&外皮节）6 种组合的双位刺激实验组与安慰剂组和空白对照组对实验室诱发痛的镇痛效果是否存在差异，结果显示，同皮节和外皮节部位使用不同频率同时进行高强度刺激的镇痛效果最好[40]，提示临床应用可采用组合刺激的方式最大化 TENS 的镇痛效果。

TENS 的镇痛效果还受刺激强度、刺激频率、刺激脉宽、刺激时长与使用频率等参数的影响[24]，且不同参数之间可能存在交互作用。实验室研究显示，感觉强烈但不致痛的刺激能够导致压痛阈限显著上升，而强度仅为触觉阈限的刺激没有导致压痛阈限的显著改变[42]。此外，动物研究显示，高频 TENS 刺激能够减弱大鼠的原发性痛觉过敏，且效果持续时间可达一天以上，但低频 TENS 刺激没有这种镇痛效应，且这种现象和刺激强度以及刺激脉宽无关[43]。然而，有研究发现当刺激强度较弱，没有达到伤害性强度时，镇痛效果可能不受刺激频率的影响，而更可能受刺激强度的影响[44]。

患者的疼痛类型、疼痛部位以及疼痛程度等对不同参数刺激的适用场景有所影响。例如，分娩痛等高强度急性痛类型不宜采用 AL-TENS 这种同样会引发不适的疼痛刺激，而适合采用常规 TENS 这种非伤害性且满意度较高的刺激[45]。对于慢性疼痛患者来说，两种刺激方式或组合刺激都可以进行尝试，但使用频次均不可过高，以免产生耐受性[46]。

1.1.2 镇痛机制

常规 TENS 的镇痛作用可通过闸门控制理论进行解释[22, 47]。该理论认为，疼痛信息是否上传取决于传导触觉和压觉的粗纤维(Aβ纤维)与传导痛觉和温觉的细纤维(Aδ和 C 纤维)的相对激活量。Aβ纤维倾向于首先激活脊髓背角中间神经元胶状质(substantia gelatinosa, SG)细胞，进而抑制二级神经元 T 细胞的激活，阻止疼痛信息的上传；而 Aδ和 C 纤维倾向于抑制 SG 细胞，进而激活二级神经元

T 细胞，促进疼痛信息的上传。常规 TENS 的强度通常强而不痛，基本不激活 Aδ 和 C 纤维，但却会激活 Aβ纤维[48]，因而可抑制疼痛信息的传导，起到镇痛作用。实证研究也证明了常规 TENS 的镇痛机制确实与闸门控制理论有关，如动物研究显示，高频低强度的 TENS 可以显著抑制多数脊髓背角神经元的自发放电，而施加低频高强度 TENS 则没有这种效应[49]。

AL-TENS 的镇痛机制与常规 TENS 有所不同。通常认为，AL-TENS 镇痛和弥漫性伤害抑制控制(diffuse noxious inhibitory controls, DNIC)产生的现象相似[50]，均和疼痛下行抑制系统[51]有关。从脑电(electroencephalograhy, EEG)实验结果来看，AL-TENS 可以引起疼痛刺激对侧感觉运动区的 alpha 振荡信号(8~12 Hz)持续增高，且该改变会增加感觉运动区和前额叶(prefrontal cortex, PFC)区域的功能连接，而 PFC 与中脑导水管周围灰质(periaqueductal gray, PAG)存在纤维投射[35]，此结果和 DNIC 诱发镇痛效应时多皮层区域投射至 PAG 的结果相匹配[52]。此外，感觉运动区和 PFC 连接的增加可能会通过内侧前额叶(medial prefrontal cortex, mPFC)到视网膜下背核(subnucleus reticularis dorsalis, SRD)的环路增强疼痛的下行抑制系统活动[35]。该系统包括 PFC、初级体表感觉皮层(primary somatosensory cortex, S1)和初级运动皮层(primary motor cortex, M1)等皮层上结构，以及 PAG 和延脑头端腹内侧区(rostral ventral medulla, RVM)等皮层下结构。具体来说，PAG 区域的谷氨酸能神经元的激活促进了 RVM 区域的 5-羟色胺(5-hydroxytryptamine, 5-HT)能神经元向脊髓背角释放 5-HT，进而促进脊髓背角中间神经元释放脑啡肽(enkephalin)和强啡肽(dynorphin)等内源性阿片物质，从而抑制脊髓背角伤害性信息的传递。研究结果也支持了疼痛下行抑制系统在 AL-TENS 镇痛中的作用。低频 TENS 不仅可以诱发阿片系统激活带来的脊髓 5-HT 释放[53]，且当阻断脊髓或 RVM 的μ阿片受体时，低频 TENS 的镇痛作用受阻[54, 55]。

1.2 tVNS

tVNS 通过激活迷走神经系统而起到镇痛作用[56]。其根据刺激位点不同，tVNS 可分为刺激颈部前外侧皮肤的颈部迷走神经电刺激(transcutaneous cervical vagus/vagal nerve stimulation, tcVNS)和刺激左耳耳甲腔或耳珠的耳部迷走神经电刺激(transcutaneous auricular vagus/vagal nerve stimulation, taVNS)。目前，tVNS 已

被证明具有良好的安全性和耐受性[57]，可用于治疗偏头痛[58, 59]和丛集性头痛[60](表 1)。

1.2.1 镇痛效果

目前针对 tVNS 缓解实验室诱发疼痛的研究较少，且研究结果不一致。例如，Busch 等发现使用频率为 20~30 Hz，脉宽为 250 μs 的方波 taVNS 对耳珠施加 65 min 痛阈下强度的刺激，可以显著降低双侧手的持续性热痛评分以及同侧手的机械痛敏感性，但是对于非疼痛刺激的探测阈限(如冷探测阈限、温探测阈限和机械探测阈限等)没有显著的影响[61]；De Icco 等发现频率为 25 Hz、强度为能引起同侧眼轮匝肌收缩的 tcVNS 刺激可以显著提高能引起下肢疼痛缩足反射的刺激阈值，而且这种效应可以延续到刺激结束后 30 min [62]。然而，Usichenko 等却发现，对耳甲腔施加频率为 8 Hz、脉宽为 200 μs 的电刺激未能改变热痛阈限；进一步的亚组分析发现，耳甲腔刺激干预组 20 名被试中只有 8 人的后测热痛阈限显著高于前测，剩下 12 人的后测热痛阈限低于前测[63]。这一结果提示 taVNS 的镇痛作用可能和个体易感性有关[63]。

目前 tVNS 的临床镇痛研究主要局限于头痛领域，很少涉及其他临床疼痛类型。Lendvai 等人总结了 2014~2018 年应用 tcVNS 治疗偏头痛和丛集性头痛的临床研究，发现 tcVNS 是一种治疗原发性头痛的安全手段，能够有效地降低丛集性头痛的发病率并减少发病时长，但是可能在偏头痛亚群体类型的应用中有偏向性[64]。tcVNS 临床使用的刺激参数相对固定，通常为持续 1 ms 的 5 kHz 正弦波脉冲(5 个正弦波，每个持续 200 μs)，脉冲频率为 25 Hz，产生 24 V 峰值电压和 60 mA 峰值输出电流[65–69]。taVNS 同样也被应用于治疗偏头痛[59]。Straube 等发现每天 4 h 的 1 Hz 电刺激可减少头痛频率，且这一刺激的效果好于 25 Hz 的刺激。此外，taVNS 也曾被应用于治疗盆骨痛[70]和慢性腰背痛[71]，但是目前相关研究数量较少。总的来说，tVNS 目前在头痛领域的应用已较为成熟，在其他疼痛类型的应用则有待进一步的研究。

1.2.2 镇痛机制

刺激迷走神经颈支或刺激迷走神经耳支均可有效引导自主神经系统功能从交感神经系统优势转向副交感神经系统优势[52, 72]。研究显示，30 Hz 的 taVNS 可

以显著降低健康志愿者心电低频能量和高频能量的比率(low frequency power/high frequency power, LF/HF)[73]，该指标的降低表明自主神经活动向副交感/迷走神经系统支配的方向移动[72]，而迷走神经系统参与了情绪的表达和相关信息处理[74]，说明激活迷走神经系统时存在调控情绪的可能。同时，脑影像研究也表明，tVNS 能够显著地影响处理和调节情绪相关信息的部分脑区的活动。例如，经过 tVNS 后杏仁核、海马、旁海马回、颞中回和颞上回活性下降，脑岛、M1 和丘脑活性增加[75]。因此，Frangos 等人推测 tVNS 可能是通过调控负性情绪调节了疼痛的不愉悦度，进而影响总体疼痛评价[76]。

tVNS 还可能直接影响了疼痛信息的传递与处理。tVNS 可能阻断了脊髓二级投射神经元对疼痛信息的传递[61]。Chandler 等将迷走神经刺激电极缠绕在猕猴的迷走神经左侧颈动脉分支，并把记录电极放置在脊髓颈段和胸段，发现迷走神经电刺激可以抑制脊髓颈段和胸段的脊髓丘脑束中的细胞活性[77]。EEG 研究显示，25 Hz 的 tcVNS 会引起 Cz 电极处 theta 频段的能量下降和 beta 频段的能量上升，以及 Oz 电极处 alpha 频段的能量下降和 gamma 频段的能量上升[78]。针对这一结果，作者认为 gamma 频段能量的上升可能反映了 tVNS 对γ-氨基丁酸能(γ-aminobutyric acid, GABA)抑制性中间神经元活动的影响[78]。

除此之外，tVNS 也可能通过部分脊髓上组织调控疼痛。从迷走神经耳支和颈支解剖投射来看，迷走神经可以投射到延髓段的三叉神经核、楔形核、孤束核以及疑核等区域[79,80]，而其中的三叉神经核与头面部的疼痛信息传递有关[81]，楔形核与疼痛信息的评价有关[82]，因此 tVNS 可能会在这些区域对疼痛信息的传递产生影响。从大脑的激活情况来看，电刺激迷走神经耳支可以激活 PAG、孤束核、中缝核、脑岛和杏仁核等脑区[83, 84]；刺激迷走神经颈支则可以激活孤束核、臂旁核、S1、脑岛以及基底神经节和额叶等区域[85]。值得注意的是，PAG、孤束核和中缝核是内源性疼痛下行调节系统的重要组成部分[86, 87]。综上，这些结果说明 tVNS 不仅可以激活疼痛下行调节系统[88]，还可能通过调节疼痛情绪来实现对疼痛的调控[61]。

2 非侵入性中枢神经电刺激镇痛

2.1 tDCS

tDCS 通过使用两个或多个电极向特定大脑区域施加直流电刺激而改变其兴奋性，进而调节相应区域的活动，起到缓解疼痛的作用[89, 90]。按电极分布的不同，tDCS 可分为三大类：双极 tDCS (bipolar/bicephalic tDCS)，单极 tDCS (monopolar/monocephalic tDCS)和高精度 tDCS (high-definition tDCS, HD-tDCS) [91]。双极 tDCS 将两个面积较大的电极置于头皮上，其中一个位于刺激的目标位置，称为刺激电极(active electrode)，另一个位于其它部位，称为返回电极(return electrode)；单极 tDCS 同样使用面积较大的刺激电极和返回电极，但返回电极不在头皮上，而在项部、肩、手臂或膝等部位；HD-tDCS 一般包含多个置于头皮的面积较小的电极，通常其中一个或多个为刺激电极，而其它为返回电极[91, 92]。疼痛研究中常用的 HD-tDCS 分为包含 1 个刺激电极和 4 个返回电极的 1 × 4 HD-tDCS [93, 94]以及包含两个刺激电极和两个返回电极的 2 × 2 HD-tDCS [95]两种。目前，这几种 tDCS 在镇痛领域都有所应用，且镇痛效果都已得到一定程度的证实[96–101] (表 2)。

2.1.1 镇痛效果

目前，tDCS 在缓解急性疼痛和慢性疼痛方面均存在大量研究。虽然有一些研究对 tDCS 的镇痛效果存在质疑[102–106]，但多数结果仍然支持 tDCS 对急性痛和慢性痛都有明显的镇痛作用[96–101]。研究显示，tDCS 可调节实验室诱发疼痛(如热痛[100]、冷痛[107]、压痛[108]和机械痛[109])，临床急性疼痛(如术后痛[110])和多种慢性痛(如肌纤维痛[111]、慢性下腰痛[112]、偏头痛[113]、脊髓损伤导致的神经病理性疼痛[114]、膝骨关节痛[115]、患肢痛[116, 117]和复杂性局部疼痛综合征[118])。目前已有多项 Meta 分析研究总结了 tDCS 对慢性疼痛的镇痛效果[119–124]。结果显示，tDCS 对不同慢性疼痛的镇痛作用存在较大的异质性，平均效应量在 0.17~1.90 之间，但总的来看，tDCS 能有效缓解慢性疼痛。

tDCS 刺激效果可能受到刺激强度、电极面积、刺激时长、电极位置、电极极性等参数的调节[91, 92]，而不同研究选取的参数往往存在较大的差异。多数研究使用的电流强度为 2 mA，电极面积为 35 cm^2，它们所施加刺激的电流密度约为

0.057 mA/cm^2。研究显示，0.03 mA/cm^2 的电流密度即可改变 M1 的兴奋性[125]。虽然理论上电流密度能影响刺激的效果[91, 92]，但绝大多数 tDCS 镇痛的研究只采用单一的电流强度和电极面积，因而缺乏足够的研究检验电流密度对 tDCS 镇痛作用的影响。

不同研究选取的刺激时长也各有不同。对于只施加 1 次刺激的研究，5~40 min [126–133]的刺激均有使用，最常见的刺激时长是 20 min。对于施加多次刺激的研究，最常见的是施加 5 次 20 min 刺激，每天施加 1 次刺激。刺激时长对 tDCS 的效果有很大的影响。有研究显示，3 min 以上的刺激才可显著改变 M1 的兴奋性[125]。正因如此，多数研究使用几十秒的短暂刺激作为对照条件以排除安慰剂效应对研究结果的干扰。不过，单次刺激时间过长还可能导致皮层兴奋性下降[134]。因此，为延长刺激效果，研究者通常采用多次刺激，而非延长单次刺激时长[91]。值得注意的是，相比常采用多次刺激调节慢性疼痛的临床研究，针对实验室诱发疼痛的 tDCS 研究多采用单次刺激[105, 131]——这可能是导致 tDCS 缓解实验室诱发疼痛的效果比缓解临床疼痛的效果略差的原因之一。然而，现有的研究较少对比刺激时长对镇痛效果的影响，更明确的结论尚待未来进一步探索。

电极位置决定了刺激作用的部位，因此是影响 tDCS 镇痛机制的关键因素。现有 tDCS 镇痛研究多将刺激电极置于 M1，返回电极则置于对侧眼眶上部，分别对应脑电电极帽 C3/C4 和 Fp2/Fp1 电极。其它常见的刺激电极位置包括背外侧前额叶(dorsal lateral prefrontal cortex, dlPFC)[100]、背侧前扣带回(dorsal anterior cingulate cortex, dACC)[103]、S1[135]等；返回电极则可置于乳突[103, 107, 136]或刺激电极对侧相应位置[137]。

电极极性是刺激部位兴奋性变化的决定性因素。通常认为，阳极刺激能够提高相应部位的兴奋性，而阴极刺激则抑制兴奋性[91, 92]。功能磁共振成像(functional magnetic resonance imaging, fMRI)研究也发现，对 M1 施加阳极刺激能够抑制疼痛相关脑区的活动，且具有明显的镇痛效果[104]。然而，对 M1 施加阴极刺激的镇痛效果仍有很大的争议[104, 109, 138]。此外，也有一些研究发现对 dlPFC 施加阴极刺激可以在一定程度上缓解疼痛[107]。这也提示 tDCS 的极性选择与刺激脑区之间存在一定的交互[93]，且 tDCS 的镇痛效果受到其它因素的影响。

2.1.2 镇痛机制

通常认为，tDCS 的作用机制是电流通过大脑组织时改变了神经细胞的兴奋性[89, 91, 92]。tDCS 使用的电流强度较弱，一般不会引起动作电位[139]，而只改变神经细胞的静息膜电位，进而调节神经细胞的兴奋性[89, 91, 92]。膜电位的变化是 tDCS 即时调节效应的生理基础[92]。阳极刺激会导致神经细胞膜去极化，进而增加兴奋性；阴极刺激导致神经细胞膜超极化，进而抑制兴奋性[140]。不过，细胞膜电位的变化难以解释 tDCS 刺激停止后的后续效用，如刺激结束后几个星期镇痛效应依然存在[141]。这一后续效应可能与神经递质活动调节了突触的连接强度有关[91,92]。研究显示，谷氨酸 NMDA 受体激动剂 *D*-环丝氨酸(*D*-Cycloserine)可延长 tDCS 对 M1 兴奋性的影响[142]，GABA 受体激动剂劳拉西泮(lorazepam)则可在短时增强和延长 tDCS 的后续效应[143]。

除了对刺激部位局部活动进行调节外，tDCS 还具有网络效应[91, 92]，能改变不同脑区之间的结构和功能连接[106, 144]。Lin 等研究显示，使用 35 cm^2 的电极对健康人左侧 dlPFC 施加 20 min 强度为 1 mA 的阳极刺激可缓解辣椒素诱发的长时疼痛，并且此镇痛作用与左侧 dlPFC-左侧丘脑连接束的各向异性分数显著相关[144]。这意味着 tDCS 的镇痛作用与左侧 dlPFC 和左侧丘脑的结构连接有关。Cummiford 等则研究显示，相较于 30 s 的对照刺激，对左侧 M1 施加 5 次、每次 20 min 的阳极刺激可降低纤维肌痛病人左侧腹外侧丘脑与内侧前额叶和左侧辅助运动区的功能连接，以及右侧腹外侧丘脑与小脑和左侧辅助运动区的功能连接[106]，而这些区域在疼痛加工和调节中起着重要作用。

需注意的是，tDCS 镇痛机制的研究依然不充分。多数研究旨在检验 tDCS 是否可缓解某种疼痛，只有少数研究利用 EEG [145]、fMRI [106, 144]和磁共振波谱[96, 146, 147]对 tDCS 镇痛的神经生理机制进行了研究。不仅如此，常用的双极 tDCS 聚焦性较差，除了激活靠近刺激电极的脑区外，还可能激活其它区域，而且返回电极处的刺激也可能产生某种生理影响，因此在推断 tDCS 镇痛机制时需谨慎[148]。单极 tDCS 和 HD-tDCS 的聚焦性比双极 tDCS 好，但它们的使用不如双极 tDCS 频繁[91, 92]，相应的机制研究也极少。未来可更多利用这两类聚焦性较好的 tDCS 技术研究其镇痛机制。

2.2 tACS

tACS 通过向大脑施加振幅和频率固定的正弦交流电流刺激来改变神经振荡信号[149, 150]，进而调节疼痛强度[19, 20]。tACS 使用的设备和 tDCS 基本相同。tACS 区别于其它经颅电刺激的关键因素是施加刺激的特性：与 tDCS 相比，tACS 施加的是正弦交流电刺激，而非强度固定的直流电刺激；与经颅随机噪声刺激(transcranial random noise stimulation, tRNS)相比，tACS 施加的是频率固定的刺激，而非频率随机变化的刺激[151]。目前针对 tACS 镇痛方面的研究较少[19, 20, 152, 153]，其镇痛效果和镇痛机制的研究尚在起步阶段(表 2)。

2.2.1 镇痛效果

tACS 缓解实验室诱发痛的效果存在一定争议。Arendsen 等探究了 tACS 调节压痛的可能性[20]。他们使用条件性学习范式，让不同视觉图形和压痛进行配对。结果显示，当视觉图形无法预测之后的压痛强度时，相较于 tRNS，对躯体感觉区(脑电电极帽上的 CP3 和 CP4 电极)施加振幅为 0.5 mA、频率为 10 Hz 的 tACS 可降低对压痛的强度和不愉悦度评分，但经过多重比较校正后便不再具有统计学意义。May 等考察了对初级躯体感觉区和前额叶施加 10 min 振幅为 0.5 mA 的 10 Hz 或 80 Hz 刺激是否可调节长时热痛，但没有发现这两类刺激可改变疼痛强度评分[153]。因此，tACS 可调节急性痛的结论依旧缺乏充分的证据，后续需开展更多相关研究。

tACS 缓解慢性疼痛的研究也十分少见。Angelakis 等报告了一个 tACS 缓解难治型特发性颈部肌张力障碍导致的疼痛的案例，该案例显示 15 Hz 的 tACS 可以有效减少患者的疼痛评分，且这种效用能够延续到刺激结束 30 天之后[152]。此外，Ahn 等开展了 tACS 缓解慢性下腰痛的随机双盲对照实验[19]。结果显示，在脑电电极帽 F3 和 F4 电极施加 40 min 振幅为 1 mA、频率为 10 Hz 的 tACS 可降低慢性下腰痛病人的疼痛强度。不仅如此，tACS 刺激还增强了躯体感觉区附近电极的 alpha 振荡信号强度，并且这种 alpha 振荡信号的增强还与疼痛强度下降显著相关。因此，tACS 可能对缓解慢性疼痛有一定作用，但未来仍需更多研究对此进行进一步验证。

2.2.2 镇痛机制

tACS 的主要作用机制在于外在施加的特定频率交流电诱发大脑产生相应频率的神经振荡信号[149, 154]。具体而言，自发的神经振荡信号与外部施加的特定频率电刺激发生神经同步化(neural entrainment)，进而导致自发神经振荡信号的频率向外部刺激频率偏移，相应频率的振幅增强、相位和外部刺激同步[155]。这一现象与外部刺激的频率和需调节的目标振荡信号的频率之间的差有关：频率差越大，神经同步的效果越差[156]。不过，tACS 也可对刺激频率的谐波起到一定的调节作用[156]。例如，10 Hz 的 tACS 刺激可调节 20 Hz 和 30 Hz 等频率的神经振荡信号。由于施加电流的方向不断反转，tACS 对神经元膜电位的影响也不断变化。在这一过程中，神经元细胞膜在超极化和去极化之间快速转换。这种细胞膜的快速变化可能调节了神经元神经冲动发放的时间模式(timing)和频率(firing rates)，最终引发神经同步化[154]。脑电研究证实了 tACS 对神经振荡信号的调节作用不仅在 tACS 刺激时存在[157]，在刺激结束后也依然存在[19, 158]，即 tACS 对神经振荡的调节不仅存在即时效应，也存在后续效应。有研究显示，20 min 的 alpha 频段刺激效果可持续 70 min [159]。然而，神经同步化的效果在撤除外部刺激后无法长久持续。tACS 的持续性后效依赖于长时程增强(long-term potentiation, LTP)和长时程抑制(long-term depression, LTD)等神经可塑性的变化[156]。

由于神经同步化效果和内源性神经振荡信号相关，镇痛研究中选取的刺激频率是与疼痛加工密切相关的神经振荡信号对应的频率，如 alpha 和 gamma 神经振荡信号[160–167]。研究显示，疼痛刺激之前的 alpha 和 gamma 频段的神经振荡信号调节个体对疼痛刺激的感知[162]，并且疼痛刺激之后 alpha 频段神经振荡信号会减弱，而 gamma 频段的神经振荡信号会增强[164]。值得关注的是，gamma 频段的神经振荡信号不受刺激新异性(saliency)的影响，而是反映了个体对疼痛强度的感知，且可编码个体内和个体间的疼痛敏感性[161, 166]。这意味着 tACS 具有调节疼痛感知的理论基础。遗憾的是，目前仍缺乏揭示 tACS 镇痛机制的直接证据。不过，Ahn 等关于 tACS 对 alpha 振荡信号的增强作用与其镇痛作用存在显著相关的发现，在一定程度上支持了 tACS 通过调节神经振荡信号从而调节疼痛感知的假设[19]。未来仍需更多研究探索 tACS 的疼痛调节作用和疼痛调节机制，尤其

是 gamma 频段 tACS 刺激对疼痛的影响。值得注意的是，gamma 频段涵盖范围较广，刺激时需考虑哪一频率或频率范围的刺激可调节疼痛。May 等的研究虽然没有发现 gamma 频段刺激对疼痛的调节作用[153]，但只选取了 80 Hz 一个频率，其它频率的刺激对疼痛的影响仍有待研究。

3 总结与展望

本文探讨了非侵入性外周电刺激(TENS、tVNS)和中枢电刺激(tDCS、tACS)的镇痛作用，并讨论了它们各自的镇痛机理。从镇痛效果来看，TENS 镇痛的相关研究已相对成熟，已应用于多种临床急性和慢性疼痛的治疗；tVNS 主要用于治疗头痛，且实验结果一致性较高；tDCS 具有全局镇痛的优点，但目前仍难以明确各类型疼痛的优化刺激脑区；tACS 的镇痛效果仅在个别研究中得到了证实，未来仍需要进一步探索。

从镇痛机制来看，四项刺激技术存在明显差异：常规 TENS 镇痛与脊髓处的闸门控制机制相关，AL-TENS 则与弥漫性伤害抑制控制机制有关；tVNS 抑制疼痛信息传递，激活疼痛下行调节系统，并可能通过调节疼痛情绪来镇痛；tDCS 改变了皮层兴奋性，调节相关神经递质的释放，并影响了与疼痛加工和调节相关的脑区的结构和功能连接；tACS 可能通过调节疼痛相关神经振荡信号改变个体的疼痛感知。

然而，神经调控电刺激技术的相关研究仍存在若干不足之处。这些局限可能是产生研究结果不一致、临床应用困难等问题的重要原因。首先，多数研究的样本量较小，每个组别的人数通常为 30 人以下。由于疼痛评分的主观性特点，个体内的疼痛感受变异性和个体间的疼痛敏感性差异以及神经电刺激的镇痛效果的个体差异都较大，在此条件下，样本量有限的研究可能导致研究结果的稳定性较差，无法可靠地揭示非侵入性神经电刺激的真实镇痛效果。未来的研究有必要逐步开展大样本、多中心的大规模研究，以检验神经电刺激镇痛效果的稳定性和可靠性。与此同时，应注意区分神经电刺激镇痛响应者(responder)和非响应者(non-responder)，探索响应者的预测因子，以进一步提高非侵入性神经电刺激的临床应用价值。

其次，目前对神经电刺激镇痛效果的研究仍不够充分、不够深入。具体而言，tVNS 研究过于局限于头痛领域，对其它疼痛类型的关注不足；tDCS 研究使用的参数较为单一，刺激参数对镇痛效果的影响不甚明确；tACS 镇痛研究尚处在起步阶段。未来有必要全面考察刺激参数对镇痛效果的调节作用，研究神经电刺激对不同疼痛类型镇痛效果的差异。

再次，神经电刺激镇痛机制仍待进一步研究。tVNS、tDCS 和 tACS 的镇痛机制不完全清晰，对镇痛机制的理解依赖于与以往其他镇痛领域发现的镇痛环路进行比较，缺乏实质性证据。同时由于部分实验设计未设置安慰剂组，只考察了电刺激神经调控前后疼痛指标的变化，因此无法排除安慰剂效应的影响。未来可以通过跨物种研究，整合微观神经元放电和神经递质释放以及宏观脑响应信号和躯体神经系统信号变化，同时通过对多实验组和安慰剂组进行量表测量或行为实验来探索相关心理因素改变，从而揭示各神经调控手段较为全面的镇痛环路。

最后，目前对不同技术组合镇痛效果的评估不足，也较少考虑神经电刺激和镇痛药物的交互作用。已有的研究侧重于检验某一项技术的镇痛效果和镇痛机制，但大多忽视了不同神经电刺激组合应用镇痛的可能性。考虑到不同外周电刺激和中枢电刺激镇痛机制的差异，整合不同技术可能会增强镇痛效果。另一方面，临床疼痛或慢性疼痛患者通常会服用镇痛药物。神经电刺激和镇痛药物的镇痛机理存在一定的共同点，因而它们之间可能存在交互作用。揭示神经电刺激和镇痛药物的复杂相互作用对这两种镇痛方式的选择都有极大的实用价值。

综上所述，克服这些局限将有力推动非侵入性神经电刺激镇痛领域的发展，促进相关技术的临床应用，最终缓解患者的疼痛，减轻疼痛对患者、家庭和整个社会的健康和经济负担。

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表 1. 外周非侵入性神经调控电刺激技术镇痛的临床应用

Table 1. Clinical application of non-invasive electrical peripheral neuromodulation techniques in pain management

Non-invasive electrical neuromodulation techniques	Clinical condition	Electrode placement	Oft-used stimulation parameters	Analgesic effects	Neural mechanisms
TENS					
Conventional TENS	CLBP[27], cancer pain[26], expulsive pain[28], primary dysmenorrhea[29, 30], postoperative pain[31] etc. More suitable for patients struggled with opioid-resistance	One active and one return electrode (60 mm × 40 mm/45 mm/90 mm); around the area of pain[24, 32]	(1) Waveform: square waves; (2) current frequency: 50–100 Hz; (3) current pulse width: 100–300 μs; (4) current intensity: strong but comfortable or muscles' motor threshold; (5) duration: 30–60 min; (6) stimulation frequency: 2–4 times per day[26–31]	(1) Size: medium; (2) duration: immediate and short-lived; (3) locality: local[22, 26–31, 47]	Gate control theory[22, 47]
AL-TENS	CLBP[36], fibromyalgia[37], postoperative pain[31] etc. More suitable for patients with chronic pain	One active and one return electrode (60 mm × 40 mm/45 mm/90 mm); at arms or legs[31, 36, 37]	(1) Waveform: square waves; (2) current frequency: 1–4 Hz; (3) current pulse width: 200–400 μs; (4) current intensity: tolerable but painful; (5) duration: 30–60 min; (6) stimulation frequency: 2–4 times per day[31, 35–38]	(1) Size: large; (2) duration: immediate and lasting; (3) locality: diffuse[31, 35–38]	(1) DNIC; (2) Activating the descending pain inhibition system[35, 50, 53–55]

tVNS					
tcVNS	Migraine[58, 60], cluster headache[58, 60]	Two electrodes; at the sternocleidomastoid muscle along the cervical branch of the vagus nerve[58 ,60]	(1) Waveform: 5 kHz sine waves; (2) current frequency: each lasting 200 μs, repeated once every 40 ms (25 Hz); (3) current intensity: highest voltage (24 V), highest intensity (60 mA); (4) duration: 20–30 min; (5) stimulation frequency: 2–3 times per day[58, 60, 64–69]	(1) Size: small; (2) duration: immediate and short-lived[58 ,60, 64–69]	(1) Indirectly modulating pain perception by regulating pain unpleasant[74–76]; (2) Decreasing the activity of second-order nociceptive neurons in the spinothalamic and spinoreticular tracts of the spinal cord[61, 77, 78]; (3) Activating the descending pain inhibition system[61, 79–88]
taVNS	Migraine[59]	One active electrode and one return electrode; at the auricular cymba and conchae, or tragus[59, 70, 71]	(1) Waveform: square waves; (2) current frequency: 1 Hz, 8 Hz, or 25 Hz; (3) current pulse width: 200–300 μs; (4) current intensity: strong but comfortable or muscles' motor threshold; (5) stimulation frequency: 4 h per day[59, 70, 71]	(1) Size: small; (2) duration: immediate and short-lived[59, 70, 71]	(1) Indirectly modulating pain perception by regulating pain unpleasant[74-76]; (2) Decreasing the activity of second-order nociceptive neurons in the spinothalamic and spinoreticular tracts of the spinal cord[61,77,78]; (3) Activating the descending pain inhibition system[61,79–88]

TENS, transcutaneous electrical nerve stimulation; CLBP, chronic low back pain; AL-TENS, acupuncture-like transcutaneous electrical nerve stimulation; DNIC, diffuse noxious inhibitory controls; tVNS, transcutaneous vagal/vagus nerve stimulation; tcVNS, transcutaneous cervical vagus/vagal nerve stimulation; taVNS, transcutaneous auricular vagus/vagal nerve stimulation.

表 2. 中枢非侵入性神经调控电刺激技术镇痛的临床应用

Table 2. Clinical application of non-invasive electrical central neuromodulation techniques in pain management

Non-invasive electrical neuromodulation techniques	Clinical condition	Electrode placement	Oft-used stimulation parameters	Analgesic effects	Neural mechanisms
tDCS					
(1) Bipolar/bicephalic tDCS **(2) Monopolar/monocephalic tDCS**	Fibromyalgia, CLBP, neuropathic pain, knee joint pain, phantom limb pain, migraine *etc*.[110–124]	One active electrode and one return electrode (35 cm^2); active electrode: at the corresponding scalp area of M1, S1, dlPFC or dACC, return electrode: at other scalp area or skin of neck, shoulder, arm, or knee[100, 103, 107, 110–125,135–137]	(1) Waveform: direct current; (2) current intensity: 2 mA; (3) duration: multiple stimulations in units of 20 min[100, 103, 107, 110–125, 135–137]	(1) Size: medium; (2) duration: immediate analgesia and lasting; (3) locality: diffuse[100, 103, 107, 110–125, 135–137]	(1) Altering the neuron excitability in pain-related cortex areas[89, 91, 92, 140]; (2) Modulating functional connectivity between brain areas[91, 92, 106, 144]
HD-tDCS	Fibromyalgia[93], pain induced by temporomandibular disorders[95]	One active electrode and four return electrodes (4×1 HD-tDCS), or two active electrodes and two return electrodes(2×2 HD-tDCS); active electrodes: at the corresponding scalp area of M1[93, 95], return electrodes: at other scalp areas	(1) Waveform: direct current; (2) current intensity: 2 mA; (3) duration: multiple stimulations in units of 20 min[93, 95]	(1) Size: large; (2) duration: immediate and lasting; (3) locality: diffuse[93, 95]	(1) Altering the neuron excitability in pain-related cortex areas[89, 91, 92, 140]; (2) Modulating functional connectivity between brain areas[91, 92, 106, 144]

tACS	CLBP[19], pain induced by intractable idiopathic cervical dystonia[152]	Two electrodes; at bilateral S1 or M1[19, 152]	(1) Waveform: sine waves; (2) current frequency: 10 Hz or 15 Hz; (3) current intensity: 0.5 mA or 1 mA[19, 157, 158]	Unsure[19, 20, 152, 153]	Modulating pain-related neural oscillations[149, 150, 154–167]

tDCS, transcranial direct current stimulation; M1, primary motor cortex; S1, primary somatosensory cortex; dlPFC, dorsal lateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; HD-tDCS, high-definition transcranial direct current stimulation; tACS, transcranial alternating current stimulation; CLBP, chronic low back pain.